phases of many outputs of the clock advance, and the amplitude of multiple rhythms is attenuated [for review, see (66, 67)]. In addition, there is an increased incidence of temporal desynchronization of two or more rhythms, fragmentation of circadian rhythms, and altered responsiveness to stimuli that induce phase shifts. Thus, declining reproductive function may be only one of many physiological endpoints to be affected by the fragmentation of the temporal organization of physiological functions.

The evidence that both the ovary and the brain are key pacemakers in menopause is compelling. We probably should not debate which component of the reproductive axis deteriorates first. It is likely that multiple redundant pacemakers govern the precise orchestration of physiological, cellular, and molecular events that weave together and lead to reproductive cyclicity. Instead, our goal should be to better understand the constellation of factors that interact to maintain regular reproductive cyclicity and how this precise dynamic balance changes with age. In so doing, we will come to understand the complex fabric of the functioning system and the multiple triggers that lead to reproductive decline.

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The Aging Immune System: Primer and Prospectus

Richard A. Miller

Changes in T lymphocyte populations underlie much of the age-related decline in the protective immune response. Aging leads to the replacement of virgin T cells by memory T cells and to the accumulation of cells with signal transduction defects. Studies of antibody gene assembly, accessory cell function, post-thymic T cell development, skewed selection of T cell receptor repertoire, and the clinical concomitants of immune senescence will shed new light on the causes and consequences of age-dependent immune failure.

Like a citadel astride key trade routes, an immune-system perspective gives a commanding view of both basic and applied gerontology. Immune cells offer powerful models for study of how aging affects gene expression, cell communication, and homeostatic regulation; few other multicellular systems perform so well in vitro after dissection and reassembly. Immune senescence also attracts intervention-minded geriatricians seeking to protect elderly patients from infection and, perhaps, from neoplasia. The past two decades of research have produced consensus in some areas, confusion in others, and provocative findings that are worth further pursuit. Figure 1 depicts some components of the immune system that exhibit age-dependent alterations.

The immune system comprises many cells with distinct functions, and the challenge to the immunogerontologist has been to map age-associated changes in immune responses to underlying cellular alterations. Aged people and rodents show declines in

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many aspects of protective immunity, including the formation of high-affinity antibodies (*1*), generation of long-lasting memory immune responses after vaccination (*2*, *3*), and expression of delayed-type hypersensitivity reactions to antigens initially encountered earlier in life (*4*). Most analytical work has relied on the convenience of short-term in vitro cultures, stimulated by polyclonal activators such as plant lectins or antibodies to T and B lymphocyte antigen receptors, but the degree to which such artificial systems mimic natural immune responses in intact animals is uncertain. Several reviews provide detailed discussions of the published literature (*5*–*7*); the goal here is to provide instead a primer on current areas of consensus and contention and a prospectus of research topics from which new ideas seem most likely to emerge.

Much of the published work describes differences between young and old immune systems, and unfortunately even the descriptive reports are often in conflict on theoretically important points (Table 1). It seems likely that age-sensitive traits, including those listed in Table 1, may also be influenced by other factors, such as diet, exercise, illness, and differences among species, strains, organs, or culture systems, in ways that confound straightforward interpretation. Only recently have investigators begun to test causal hypotheses and to seek mechanistic connections between immune senescence and other components of the aging process.

Changes in T Lymphocyte Function

T cell proliferation tends to decline with donor age, whether measured in vitro in mitogen-stimulated cultures or in vivo as delayed-type hypersensitivity responses. Generation of cytotoxic effectors and provision of help for B cell proliferation and maturation also tend to decline with age [reviewed in (*6*)]. Production of interleukin-2 (IL-2) by T cells, a key factor in all three of these cell-mediated responses, declines with age in both mice and humans (*8*–*10*). Because generation of high-affinity IL-2 receptors after stimulation is also lower in T cells from older individuals (*11*), supplemental IL-2 by itself can in most cases produce only partial restoration of T cell responses in culture. Indeed, defects in both IL-2 and IL-2 receptor gene expression probably reflect two underlying factors: a shift from naïve to memory T cells and alterations in the early stages of T cell signal transduction. Most T cells in young adults resemble the "naïve" cells freshly emigrated from the thymus to the peripheral immune organs, but aging leads to a shift away from naïve cells to a relative increase in the antigen-experienced memory subsets (*12*–*14*). In mice, the shift in subsets largely accounts for the age-related decline in responsiveness to mitogen in vitro (*12*) and could plausibly contribute to the parallel decline with age in in vivo responsiveness to newly encountered antigens.

Although T cells with the surface characteristics of memory cells increase with age, it is still unclear whether the function of these cells is impaired by aging. Some cytokines preferentially secreted by memory T cells, such as IL-4 and IL-10, are reported to be produced at greater concentrations by T cells from old mice (*13*, *15*), although there are also conflicting data on IL-4 from mice (*16*) and humans (*17*). Reports on age-related changes in the production of other cytokines typically produced by memory T cells, such as interferon-γ (IFN-γ), are also mutually inconsistent (*6*). Memory responses induced by vaccination are typically longer lasting in young than in old people (*2*). Age-dependent accumulation of specialized T cells within the memory cell pool, such as those marked by increased expression of P-glycoprotein (*18*), might contribute to age-dependent loss of memory T cell function.

The poor responses of T cells from older donors may reflect changes in signal transduction pathways. T cells from aged mice show defects in calcium mobilization (*19*, *20*) and protein phosphorylation (*21*) within the first 5 min after contact with an activating stimulus. Aging leads to declines in mitogen-stimulated phosphorylation that are attributable to both tyrosine-specific (*22*) and serine-threonine–specific (*21*, *23*, *24*) kinases. Some data suggest qualitative changes in substrate or kinase compartmentalization. Isoforms of protein kinase C (PKC), for example, are distributed differently in T cells isolated from old or young humans (*24*), and activation of PKC by phorbol myristate ace-

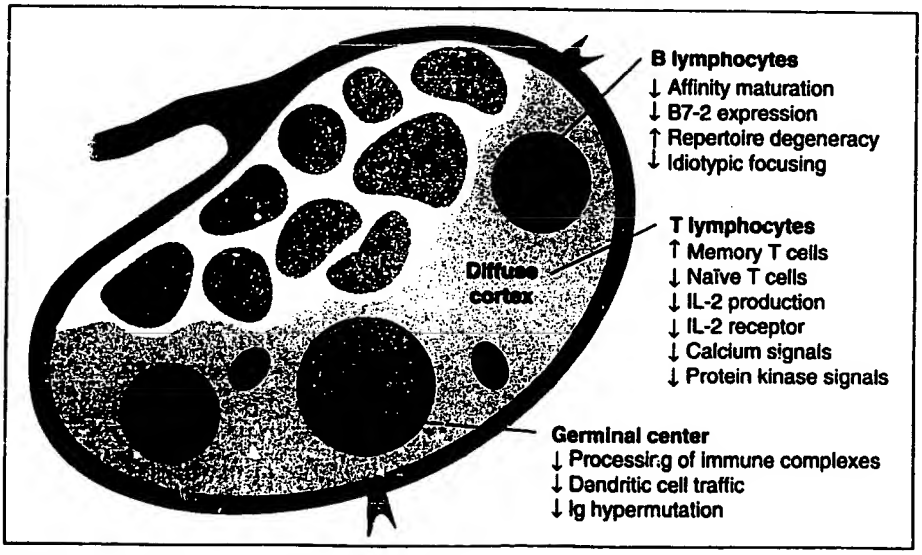

Fig. 1. Key areas of immunological change in old age.

Table 1. Examples of controversial observations from the phenomenological literature. In most of these cases, there are several published reports on each side of the controversy. Additional citations can be found in (*6*). PBLs, peripheral blood lymphocytes.

Observation	Seen in	Reference
CD4/CD8 ratio increases with age	Human PBLs	(*71*)
CD4/CD8 ratio decreases with age	Human PBLs	(*72*)
IL-4 production increases with age	Mouse spleen	(*13*)
IL-4 production decreases with age	Human PBLs	(*17*)
IFN-γ production increases with age	Human PBLs; mRNA and protein	(*73*)
IFN-γ production decreases with age	Human PBLs; mRNA	(*74*)
NK activity declines with age	Mice, internal lymphoid tissue	(*44*)
NK activity is unchanged with age	Human PBLs	(*45*)
Ig: change <30%	Human serum; multiple isotypes	(*75*)
Ig: two- to sixfold increases	Mouse serum; multiple isotypes	(*76*)
Ig: little change	Mouse serum; multiple isotypes	(*77*)

tate leads to different patterns of protein phosphorylation in T cells from young and old mice (*21*). Phosphorylation of SHC, a coupling protein implicated in Ras activation, declines with age in T cells stimulated by antibodies to the CD3 chains of the T cell antigen receptor complex but shows an age-related increase in mouse T cells activated with antibodies to the CD4 receptor (*25*), which suggests an age-dependent alteration in distribution or regulation of $pp56^{lck}$, the tyrosine-specific protein kinase linked to the CD4 molecule.

Changes in B Lymphocyte Function

Although there is a clear loss with age in the ability to produce antibody in response to new or previously encountered antigens, it is uncertain to what extent this decline reflects intrinsic changes in B cell function (*6*, *26*). Age-related changes in B cell responsiveness, measured in vitro as proliferation or as antibody production, are often subtle and inconsistent (*6*). Much of the decline in humoral immunity is a result of changes in the activities of T cells needed to promote B cell activation and differentiation (*27–30*), including T cell expression of CD40L, a key factor in contact-dependent B cell activation through the cell surface CD40 protein (*29*). Age leads to an increase in the serum concentrations of autoantibodies (*31*, *32*), but these are typically of low titer and of unknown pathological significance. The relative use of different antibody gene families changes little with age (*33*), but there are well-documented cases of antigen-specific responses in which antibody gene families not used in young mice are unexpectedly activated in old mice (*34*, *35*); in at least one such case, the antibodies produced are less able to protect against pneumococcal infection (*36*). The use of these atypical immunoglobulin (Ig) genes in specific antibody responses depends on the activities of T cells that are present in old but not in young mice (*30*). Direct sequencing of antibody cDNAs has suggested that aging may lead to changes in the lengths of D-region gene fragments incorporated into the mature antibody mRNA (*37*). Duplicate sequences are frequently encountered in a sample of antibodies from old mice, suggesting that aging may lead to a repertoire partially dominated by fairly small numbers of expanded B cell clones (*37*). Hypermutation, which greatly increases antibody diversity in immune reactions of young mice, seems not to occur in the germinal centers of older animals (*38*), perhaps due to a defect in expression of the B7-2 molecule through which B cells receive signals from the T cell surface molecule CD28 (*39*). Defects in both T and B cells seem to contribute to the age-related decline in antibody hypermutation (*30*).

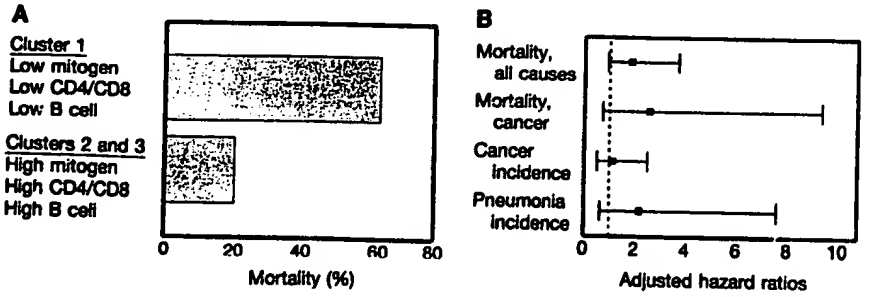

Fig. 2. Associations between immune responsiveness and life-span in mice and humans. (**A**) Differential mortality risks in groups of healthy, very old Swedes (aged 86 to 92 years at the time of immune testing), sorted by clusters analysis into groups with different patterns of immune status indices. Individuals in cluster 1 (n = 14) exhibited low mitogen responses, low CD4 cells, high CD8 cells, and low B cells, and were more likely to die in a 2-year follow-up period as compared with those in clusters 2 and 3 (n = 75, P = 0.0008). [Adapted from (*63*)] (**B**) Age-adjusted hazard ratios for various adverse events in a group of 74 anergic (but apparently healthy) and 155 nonanergic people, aged 60 or older, who were followed from 1979 to 1988. A value greater than 1 (dotted line) indicates an increased risk in anergic individuals. The boxes indicate ratios (anergic/nonanergic), and the error bars represent 95% confidence intervals. [Adapted from (*64*)] (**C**) Each point shows life-span and antibody titer for 10 or 11 genetically heterogeneous mice grouped by life-span decile. Mice were immunized at 60 days of age, and the titer of mercaptoethanol-resistant IgG antibody to sheep erythrocyte was measured 7 days later. [Adapted from (*68*)]

Accessory Cell Function

Most studies of accessory cell function have found little evidence for an effect of age on such cells' ability to support T or B cell activation in mitogen- or antibody-stimulated cultures (*6*). Studies of macrophage cytokine production have yielded inconsistent results, with the size and even the direction of the aging effect being dependent on variations in stimulus, culture duration, and cytokine assayed (*40*). Changes in the ability of the follicular dendritic cell to process and present antigen-containing immune complexes may contribute to the decline of germinal center formation and secondary immune responses in old mice (*41*). Defects in the transport of antigen into lymph node germinal centers by migrating dendritic cells (*42*) may also contribute to diminished humoral and cell-mediated immunity.

Natural Cytotoxicity

Studies of natural killer (NK) cell function in humans and mice have produced a provocative discrepancy. Mouse studies, almost invariably using spleen- and lymph node–derived NK cells, show a profound loss of NK cell function in older animals (*43*, *44*). Tests for human NK cell function, invariably involving peripheral blood-derived cells rather than cells from internal lymphoid tissues, show little if any age effect (*45*, *46*). The single study to describe the effect of age on mouse blood NK cell function (*47*) generated results concordant with the studies of human blood, finding little or no age effect. The contrast between the data derived from blood and from internal lymphoid tissue suggests that NK cell activity in spleen and lymph node tissues might be age-sensitive in humans as it is in mice. The hypothesis that a loss of internal NK cell activity contributes to increasing sensitivity to neoplastic and viral illnesses in older people will remain speculative until data become available on NK cell function in the human spleen and lymph nodes.

Changes in T Cell Receptor Repertoire

Although initial studies using cDNAs pooled from multiple animals suggested that aging led to little alteration in the expressed repertoire of T cell receptor genes (*48*), more recent studies, which avoided pooling of samples across donors, have begun to challenge the previous view. Many middle-aged and older mice exhibit expansions of T cells that are detectable by staining with antibodies specific for individual T cell receptor variable-region gene families (*49*). These ex-

pansions are idiosyncratic, in the sense that individual mice differ in the specific variable-region genes used by the expanded clone or clones. Similar expansions have been noted in human T cells from adult donors (*50–52*), but there is little information about the effects of age on T cell clonal predominance in humans, except that expanded clones seem not to be present in cord blood (*50, 52*). In both species, the clonal expansion is restricted to the subset of T cells that expresses the CD8 surface marker and is specialized for detection of antigen presented by class I histocompatibility proteins. Mice raised under specific pathogen-free conditions are less likely to exhibit such clonal idiosyncrasy (*49*). At least in humans, the expanded clones typically fail to express CD28, a surface receptor needed for functional T cell activation (*50*), and it is therefore provocative to note that CD28 expression is also lost in cultured T cells that have undergone many rounds of in vitro proliferation (*53*). It is not yet clear whether expanded cell clones found in vivo are functional or anergic, nor whether they might have specialized activities that contribute to age-related immunological deficits. Expansion of certain T cell clones at the expense of others may diminish the functional repertoire of the immune system at older ages and thus limit the ability to respond to novel immunogens.

T Cell Development

The dramatic morphological evidence for thymic involution in early adult life has traditionally been deemed responsible for T cell immune senescence, and indeed thymic export declines by 90% in the first quarter of the life-span (*54*), but improved quantitative understanding of the relations among T cell emigration, proliferation, and removal suggest strongly that more dynamic models of post-thymic development will be needed to account for the senescent changes in T cell populations in adults. The rate of thymic emigration during adult life, about 10^5 per day in 6-month-old mice (*54*), is only a small fraction of the rate needed to account for the reported turnover rate of peripheral T cells, which is about 3×10^7 per day (*55*). This disparity suggests that the relative stability of T cell numbers across the life-span is regulated by a balance between cell death and renewal from mature thymic-processed progenitors. Peripheral T cells are capable, in the absence of thymic influence, of at least 10^5-fold expansion in vivo (*56*). It is not clear whether the peripheral immune system might contain one or more cell types with a special propensity for self-renewal, although both in vitro clonal analysis (*57*) and in vivo repopulation studies (*58*) suggest that not all peripheral T cells are equally endowed with a capacity for extensive and prolonged clonal expansion. Antigen-driven expansion after immunization or infection is typically followed by the death of 97% of the antigen-specific T cells (*59*), but the factors that control, for each cell, the decision among various outcomes—continued proliferation, differentiation into terminal effectors, survival as memory cells, or apoptotic death—are poorly understood. The mean telomere lengths of both naïve and memory human T cells shorten in parallel during adult life at a rate consistent with an average turnover of about 0.3 population doublings each year (*60*); further work on T cell subsets and heterogeneity will be needed to see whether the T cell pool contains outliers with special capabilities for self-renewal. Activation-induced apoptosis of T cells has been reported variously either to increase (*61*) or decrease (*62*) with donor age. Old transgenic mice in which T cells constitutively express the apoptosis-promoting ligand Fas are reported to retain the T cell proliferation and cytokine production of youth (*62*); this finding, once confirmed and extended, may yield further insight into the pathways that regulate the balance and functional capacity of age-sensitive T cell subsets.

Immunosenescence, Disease, and Survival

Many groups have attempted to test the idea that immune status can serve as a useful indicator of general health or "biological age" and provide prognostic information about survival and disease risk. Early studies of human populations (*6*) provided suggestive evidence of a relation between immune function and mortality risk but failed to meet the technical challenges of adequate control over possible confounders (such as age and preexisting illness). Recent work (Fig. 2A) suggests that a combination of immune status indices, including high T cell proliferation, high B cell number, and a relatively low ratio of CD8 to CD4 cells, can indeed predict survival over a 2-year follow-up interval in very old people (age range 86 to 92 years) (*63*). Anergy in skin tests for delayed-type hypersensitivity may also provide a good indicator of subsequent mortality (Fig. 2B) (*64*). A longitudinal analysis of individuals known to be free of detectable illness has shown that a decline in peripheral blood lymphocyte count is associated with diminished 1-year survival (*65*), but this study unfortunately did not include any information about lymphocyte subsets or immune function.

The comparatively long life-span of humans greatly complicates analysis of the clinical consequences of age-related changes in immune competence, but three studies of immunity in mice have provided supportive evidence that the extent or pace of immune change may be associated, perhaps causally, with diminished survival. In one case, mice with comparatively high levels of $CD8^+$ T cells were found to have short survival (*66*). In a second instance, high numbers of memory T cells at 6 months of age were associated with a high risk of early mortality (*67*). Lastly, high concentrations of induced antibody production were associated with long life-span and low tumor incidence in a backcross generation derived from mouse stocks that had been selectively bred for differences in humoral immune function (*68*) (Fig. 2C). Analysis of variance in the F_1 and F_2 crosses suggests that as few as three to nine loci (or groups of closely linked loci) may be responsible for interanimal differences in life-span and antibody production (*68*). Mapping studies associating polymorphic microsatellite markers with humoral immunity in early life have shown that three of the segregating loci are linked to genes known to play major roles in immune function: the major histocompatibility region H-2, the immunoglobulin region IgH, and the section of chromosome 6 that includes the CD8 locus (*69*), with preliminary evidence that implicates additional loci on chromosomes 4 and 8. H-2–associated variations in survival among inbred mouse lines have also been reported (*70*). A demonstration that alleles at immunoregulatory loci influence life-span and tumor incidence in segregating stocks would provide a strong rationale for additional genetic and mechanistic analyses of the links connecting immune function to cancer and other forms of late-life illness.

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78. I thank G. Kelsoe and N. Klinman for comments on a draft of this paper. Work in my laboratory is supported by grants from the National Institute on Aging and from the Allied Signal Foundation.